ClinicalEvidence

Fungal toenail infections

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ABSTRACT

INTRODUCTION: Fungal infections are reported to cause 23% of foot diseases and 50% of nail conditions in people seen by dermatologists, but are less common in the general population, affecting 3% to 5% of people. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of oral treatments for fungal toenail infections? What are the effects of topical treatments for fungal toenail infections? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2011 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 12 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: amorolfine, butenafine, ciclopirox, fluconazole, griseofulvin, itraconazole, ketoconazole, mechanical debridement, terbinafine, and tioconazole.

QUESTIONS

What are the effects of oral treatments for fungal toenail infections?. 3

What are the effects of topical treatments for fungal toenail infections?. 17

INTERVENTIONS

ORAL TREATMENTS

Beneficial

Itraconazole (oral) (more effective than placebo, but probably less effective than terbinafine) 3

Terbinafine (oral) 7

Likely to be beneficial

Fluconazole (oral) (although benefits are modest, even after long-term treatment) 10

Unknown effectiveness

Griseofulvin (oral) 12

Ketoconazole (oral) 16

TOPICAL TREATMENTS

Likely to be beneficial

Ciclopirox (topical) (although benefits are modest, even after long-term treatment) 17

Unknown effectiveness

Amorolfine (topical) 19

Butenafine (topical) 20

Fluconazole (topical) 20

Ketoconazole (topical) 21

Mechanical debridement 19

Terbinafine (topical) 21

Tioconazole (topical) 21

Key points

- Fungal toenail infection (onychomycosis) is characterised as infection of part or all of the toenail unit, which includes the nail plate, the nail bed, and the nail matrix. Over time, the infection causes discoloration and distortion of part or all of the nail unit.

  Fungal infections are reported to cause 23% of foot diseases and 50% of nail conditions in people seen by dermatologists, but are less common in the general population, affecting 3% to 5% of people.

  Infection can cause discomfort in walking, pain, or limitation of activities.

- People taking oral antifungal drugs reported greater satisfaction, and fewer onychomycosis-related problems, such as embarrassment, self-consciousness, and being perceived as unclean by others, compared with people using topical antifungals.

  Oral antifungals have general adverse effects including gastrointestinal complaints (such as diarrhoea), rash, and respiratory complaints. It was rare for people to withdraw from an RCT because of adverse effects.

- Both oral itraconazole and oral terbinafine effectively increase cure rates; terbinafine seems slightly more effective.

  Adverse effects unique to terbinafine include sensory loss, such as taste, smell, or hearing disturbance.

- Alternative oral antifungal treatments include fluconazole, which seems to modestly improve cure rates, and ketoconazole and griseofulvin, which may be effective; but the evidence is insufficient to allow us to say for certain.

- Topical ciclopirox seems to modestly improve symptoms compared with placebo.

  We found no evidence examining the effectiveness of other topical agents such as ketoconazole, fluconazole, amorolfine, terbinafine, tioconazole, or butenafine.

We don't know whether mechanical debridement has any effect on fungal toenail infection, as we found no adequate studies.

DEFINITION

Fungal toenail infection (onychomycosis) is characterised as infection of part or all of the nail unit, which includes the nail plate, the nail bed, and the nail matrix. [1] [2] [3] Over time, the infection causes discoloration and distortion of part or all of the nail unit. [4] The tissue under and around the nail may also thicken. This review deals exclusively with dermatophyte toenail infections (see aetiology) and excludes candidal or yeast infections.

INCIDENCE/ PREVALENCE

Fungal infections are reported to cause 23% of foot diseases and 50% of nail conditions in people seen by dermatologists, but are less common in the general population, affecting 3% to 5% of people. [3] The prevalence varies among populations, which may be due to differences in screening techniques. In one large European project (13,695 people with a range of foot conditions), 35% had a fungal infection diagnosed by microscopy/culture. [5] One prospective study in Spain (1000 adults aged >20 years) reported a prevalence of fungal toenail infection as 2.7% (infection defined as clinically abnormal nails with positive microscopy and culture). [6] In Denmark, one study (5755 adults aged >18 years) reported the prevalence of fungal toenail infection as 4.0% (determined by positive fungal cultures). [7] The incidence of mycotic nail infections may have increased over the past few years, perhaps because of increasing use of systemic antibiotics, immunosuppressive treatment, more advanced surgical techniques, and the increasing incidence of HIV infection. [8] However, this was contradicted by one study in an outpatient department in Eastern Croatia, which compared the prevalence of fungal infections between two periods (1986–1988, 47,832 people; 1997–2001, 75,691 people). [9] It found that the prevalence of fungal infection overall had increased greatly over the 10 years, but that the percentage of fungal infections affecting the nails had decreased by 1% (fungal infections overall: 0.26% in 1986–1988 *v* 0.73% in 1997–2001; nail: 10.31% in 1986–1988 *v* 9.31% in 1997–2001).

AETIOLOGY/ RISK FACTORS

Fungal nail infections are most commonly caused by anthropophilic fungi called dermatophytes. The genera *Trichophyton*, *Epidermophyton*, and *Microsporum* are typically involved, [1] specifically *T rubrum*, *T mentagrophytes* var *interdigitale*, and *E floccosum*. Other fungi, moulds, or yeasts may be isolated, such as *Scopulariopsis brevicaulis*, *Aspergillus*, *Fusarium*, and *Candida albicans*. [3] *T rubrum* is now regarded as the most common cause of onychomycosis worldwide. [10] Several factors that increase the risk of developing a fungal nail infection have been identified. One survey found that 26% of people with diabetes had onychomycosis, and that diabetes increased the risk of infection, but the type and severity of diabetes was not correlated with infection (OR 2.77, 95% CI 2.15 to 3.57). [11] Another survey found that peripheral vascular disease (OR 1.78, 95% CI 1.68 to 1.88) and immunosuppression (OR 1.19, 95% CI 1.01 to 1.40) increased the risk of infection. These factors may explain the general increase in prevalence of onychomycosis in the older population. [12] Environmental exposures such as occlusive footwear or warm, damp conditions have been cited as risk factors, as has trauma. [2] [12] Fungal skin infection has been proposed as a risk factor. [3] [10] [12] However, one large observational study, which included 5413 people with positive mycology, found that only a small proportion (21.3%) had both skin and toenail infections. [12]

PROGNOSIS

Onychomycosis does not have serious consequences in otherwise healthy people. However, the Achilles project (846 people with fungal toenail infection) found that many people complain of discomfort in walking (51%), pain (33%), or limitation of their work or other activities (13%). [5] Gross distortion and dystrophy of the nail may cause trauma to the adjacent skin, and may lead to secondary bacterial infection. In immunocompromised people, there is a risk that this infection will disseminate. Quality-of-life measures specific to onychomycosis have been developed. Studies using these indicators suggest that onychomycosis has negative physical and psychosocial effects. [13] [14] [15]

AIMS OF INTERVENTION

To eradicate fungal spores from the nail unit (nail bed, matrix, or plate); to allow a normal nail to regrow if permanent damage to the nail matrix has not occurred.

OUTCOMES

Cure rates; negative microscopy and culture; **patient satisfaction** with treatment; **adverse effects** of treatment, especially liver failure.

METHODS

Clinical Evidence search and appraisal March 2011. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2011, Embase 1980 to March 2011, and The Cochrane Database of Systematic Reviews, Issue 1, 2011. An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information

specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. RCTs of treatment in fingernails and of infections related to candidal and yeast infections were also excluded. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. We also considered observational studies for harms because of the potentially serious nature of the harms (liver failure). In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 24). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of oral treatments for fungal toenail infections?

OPTION ITRACONAZOLE (ORAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- Oral itraconazole effectively increases cure rates of fungal toenail infection.
- People taking oral antifungal drugs reported greater satisfaction, and fewer onychomycosis-related problems, such as embarrassment, self-consciousness, and being perceived as unclean by others, compared with people using topical antifungals.
- Oral antifungals have general adverse effects including gastrointestinal complaints (such as diarrhoea), rash, and respiratory complaints. It was rare for people to withdraw from an RCT because of adverse effects.

Benefits and harms

Oral itraconazole versus placebo:

We found one systematic review (search date 2000). [16]

Cure rates

Compared with placebo Oral itraconazole may be more effective at curing fungal toenail infection (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[16] Systematic review	433 people with fungal toenail infection 3 RCTs in this analysis	**Cure rates , 12 weeks** 63% with oral itraconazole (200 mg/day) 4% with placebo Absolute numbers not reported	ARI 60% 95% CI 54% to 67%	○○○	oral itraconazole

Patient satisfaction

No data from the following reference on this outcome. [16]

Adverse effects

No data from the following reference on this outcome. [16]

Oral itraconazole versus oral griseofulvin:

See option on oral griseofulvin, p 12 .

Oral itraconazole versus oral terbinafine:

We found one systematic review (search date 2000, 4 RCTs) [16] and one subsequent RCT. [17]

Cure rates

Oral itraconazole compared with oral terbinafine Oral itraconazole may be less effective than oral terbinafine at curing fungal toenail infection after 12 to 16 weeks' treatment (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[16] Systematic review	501 people with fungal toenail infection 2 RCTs in this analysis	**Cure rates , 1 year** 48% with oral itraconazole (200 mg/day) 69% with oral terbinafine (250 mg/day) Absolute numbers not reported	ARI 21% 95% CI 13% to 29%	○○○	oral terbinafine
[16] Systematic review **3-armed trial**	60 people with fungal toenail infection Data from 1 RCT The remaining arm assessed pulsed terbinafine (500 mg/day for 1 week in every 4 weeks)	**Cure rates , 43 weeks** 75% with pulsed itraconazole (400 mg/day for 1 week in every 4 weeks) 84% with continuous terbinafine (250 mg/day for 12 weeks) Absolute numbers not reported	ARI +9% 95% CI –34% to +16%	⟷	Not significant
[16] Systematic review **4-armed trial**	250 people with fungal toenail infection Data from 1 RCT The remaining arms assessed pulsed itraconazole for 16 weeks (regimen as for 12-week treatment) and continuous terbinafine (250 mg/day for 16 weeks)	**Cure rates , 12 weeks** 33% with itraconazole for 12 weeks (400 mg/day for 1 week in every 4 weeks) 65% with continuous terbinafine (250 mg/day for 12 weeks) Absolute numbers not reported	ARI 33% 95% CI 21% to 44%	○○○	terbinafine
[16] Systematic review **4-armed trial**	246 people with fungal toenail infection Data from 1 RCT The remaining arms assessed itraconazole for 12 weeks	**Cure rates , 16 weeks** 43% with pulsed itraconazole for 16 weeks (regimen as for 12-week treatment) 67% with continuous terbinafine (250 mg/day for 16 weeks) Absolute numbers not reported	ARI 25% 95% CI 13% to 37%	○○○	terbinafine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	(400 mg/day for 1 week in every 4 weeks) and continuous terbinafine (250 mg/day for 12 weeks)				
[17] RCT	70 people with diabetes and dermatophyte toenail distal and lateral subungual onychomycosis	**Cure rates , 48 weeks** 30/35 (88%) with oral pulsed itraconazole (200 mg twice daily, 1 week on/3 weeks off for 12 weeks) 23/29 (77%) with oral terbinafine (250 mg/day for 12 weeks)	ARI +11.5% 95% CI –5.2% to +28.2%	⟷	Not significant

Patient satisfaction

No data from the following reference on this outcome. [16] [17]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] RCT	70 people with diabetes and dermatophyte toenail distal and lateral subungual onychomycosis	**Gastric pain** with oral pulsed itraconazole (200 mg twice daily, 1 week on/3 weeks off for 12 weeks) with oral terbinafine (250 mg/day for 12 weeks) The RCT reported that only 1 person in the itraconazole group withdrew because of gastric pain. There were no other serious adverse events or interactions with normal medications			

No data from the following reference on this outcome. [16]

Oral itraconazole versus oral ketoconazole:
We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral itraconazole versus oral fluconazole:
We found one systematic review (search date 2000), which identified no RCTs. [16]

Pulsed versus continuous itraconazole:
We found one systematic review (search date 2000, 3 RCTs). [16]

Cure rates

Pulsed oral itraconazole compared with continuous oral itraconazole Pulsed oral itraconazole for 3 to 4 months and continuous oral itraconazole may be equally effective at curing fungal toenail infection (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[16] Systematic review	121 people with fungal toenail infection Data from 1 RCT	**Cure rates , 52 weeks** 66% with continuous itraconazole (200 mg/day) for 12 weeks 69% with pulsed itraconazole (400 mg/day for 1 week in every 4 weeks) for 12 weeks Absolute numbers not reported	ARI +3% 95% CI –10% to +20%	⟷	Not significant
[16] Systematic review	50 people with fungal toenail infection	**Cure rates , 3 to 4 months** 64% with 3 months' pulsed itraconazole (400 mg/day for 1 week in every 4 weeks) 72% with 4 months' pulsed itraconazole (400 mg/day for 1 week in every 4 weeks) Absolute numbers not reported	ARR +8% 95% CI –20% to +30%	⟷	Not significant
[16] Systematic review	64 people with fungal toenail infection	**Cure rates , 12 weeks** 68% with continuous itraconazole (200 mg/day) for 12 weeks 50% with pulsed itraconazole (200 mg/day for 1 week in every 4 weeks) for 12 weeks Absolute numbers not reported	ARR +18% 95% CI –50% to +40%	⟷	Not significant
[16] Systematic review	64 people with fungal toenail infection	**Cure rates , 16 weeks** 64% with continuous itraconazole (200 mg/day) for 16 weeks 64% with pulsed itraconazole (200 mg/day for 1 week in every 4 weeks) for 16 weeks Absolute numbers not reported	ARR 0% 95% CI –34% to +34%	⟷	Not significant

Patient satisfaction

No data from the following reference on this outcome. [16]

Adverse effects

No data from the following reference on this outcome. [16]

Oral itraconazole versus topical treatments:

We found no systematic review or RCTs. We found one longitudinal study comparing oral antifungals versus topical treatments (see comment on oral griseofulvin, p 12).

Further information on studies

[16] Outcomes were measured at 12 weeks. It is more clinically relevant to measure outcomes after at least 9 months, because it takes at least 6 months for the toenail to regrow completely.

Comment: See comment on oral griseofulvin, p 12 .

Re-infection rates:
One open-label RCT comparing oral itraconazole (400 mg/day for 1 week in every 4 for 12 weeks) versus oral terbinafine (250 mg/day for 12 weeks) recorded the number of people initially considered cured (mycological cure) who then became re-infected with either the same or a different fungal species during the course of the study (relapsed). [18] At the final follow-up (96 weeks), 21% of people in the itraconazole group versus 14% in the terbinafine group were found to have a further infection. This was reported to be non-significant (P >0.05). [18]

OPTION TERBINAFINE (ORAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- Oral terbinafine effectively increases cure rates of fungal toenail infection.
- People taking oral antifungal drugs reported greater satisfaction, and fewer onychomycosis-related problems such as embarrassment, self-consciousness, and being perceived as unclean by others, compared with people using topical antifungals.
- Oral antifungals have general adverse effects including gastrointestinal complaints (such as diarrhoea), rash, and respiratory complaints. It was rare for people to withdraw from an RCT because of adverse effects.

Benefits and harms

Oral terbinafine versus placebo:

We found one systematic review (search date 2000, 5 RCTs). [16] The review identified two RCTs, which could not be included in the meta-analysis because they examined different terbinafine regimens. We therefore report their results individually below.

Cure rates

Compared with placebo Oral terbinafine for 12 to 24 weeks may be more effective at curing fungal toenail infection (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[16] Systematic review	337 people with fungal toenail infection 3 RCTs in this analysis	**Cure rates , 12 weeks** 63% with oral terbinafine 20% with placebo Absolute numbers not reported	ARI 43% 95% CI 34% to 53%	○○○	oral terbinafine
[16] Systematic review	353 people with fungal toenail infection Data from 1 RCT	**Cure rates , 12 weeks** 70% with oral terbinafine (250 mg/day) 8% with placebo Absolute numbers not reported	ARI 62% 95% CI 52% to 72%	○○○	oral terbinafine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[16] Systematic review	353 people with fungal toenail infection Data from 1 RCT	**Cure rates , 24 weeks** 87% with oral terbinafine (250 mg/day) 8% with placebo Absolute numbers not reported	ARI 79% 95% CI 70% to 87%	○○○	oral terbinafine
[16] Systematic review	109 people with fungal toenail infection Data from 1 RCT	**Cure rates , 12 weeks** 38% with oral terbinafine (250 mg/day) 0% with placebo Absolute numbers not reported	ARI 38% 95% CI 20% to 50%	○○○	oral terbinafine
[16] Systematic review	109 people with fungal toenail infection Data from 1 RCT	**Cure rates , 16 weeks** 37% with oral terbinafine (250 mg/day) 0% with placebo Absolute numbers not reported	ARI 37% 95% CI 21% to 56%	○○○	oral terbinafine
[16] Systematic review	109 people with fungal toenail infection Data from 1 RCT	**Cure rates , 24 weeks** 65% with oral terbinafine (250 mg/day) 0% with placebo Absolute numbers not reported	ARR 65% 95% CI 46% to 81%	○○○	oral terbinafine

Patient satisfaction

No data from the following reference on this outcome. [16]

Adverse effects

No data from the following reference on this outcome. [16]

Oral terbinafine versus griseofulvin:

See option on oral griseofulvin, p 12 .

Oral terbinafine versus oral itraconazole:

See option on oral itraconazole, p 3 .

Oral terbinafine versus oral ketoconazole:

We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral terbinafine versus oral fluconazole:

We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral terbinafine versus topical treatment:

We found one RCT comparing three treatments. [19] We also found one longitudinal study comparing oral antifungals versus topical treatments (see comment on oral griseofulvin, p 12). We found one case report of hepatotoxicity associated with terbinafine. [20]

Cure rates

Oral terbinafine alone compared with oral terbinafine plus topical ciclopirox Continuous terbinafine alone for 12 weeks and pulsed or continuous terbinafine for 12 weeks plus topical ciclopirox for 48 weeks may be equally effective at curing fungal toenail infection (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[19] RCT **3-armed trial**	73 people with fungal toenail infection	**Cure rates , 48 weeks** 14/21 (67%) with topical ciclopirox daily for 48 weeks plus pulsed terbinafine for the initial 12 weeks (250 mg daily for 4 weeks daily/4 weeks rest/4 weeks daily) 19/27 (70%) with topical ciclopirox plus continuous terbinafine for 12 weeks followed by topical ciclopirox alone for 36 weeks 14/25 (56%) with continuous terbinafine alone for 12 weeks	Reported as not significant P value not reported	⟷	Not significant

Patient satisfaction

No data from the following reference on this outcome. [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT **3-armed trial**	73 people with fungal toenail infection	**Proportion of people reporting adverse effects** 21% with ciclopirox plus pulsed terbinafine 21% with ciclopirox plus continuous terbinafine 22% with continuous terbinafine alone Absolute numbers not reported Adverse events included gastrointestinal effects and subcutaneous tissue and skin disorders	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20]	One 48-year-old woman with onychomycosis	**Hepatotoxicity** with terbinafine 250 mg daily for 5 days with no terbinafine Case report of occurrence of fulminant hepatic failure after taking terbinafine; see further information on studies for full details	No significance assessment between groups performed		

Further information on studies

[20] The woman developed fulminant hepatic failure over a period of 4 weeks, and subsequently required liver transplantation. Histological examination reported tissue status compatible with a drug-related cause of disease. The woman additionally took dosulepin 75 mg daily and propranolol 40 mg twice daily.

[16] Outcomes were measured at 12 weeks. It is more clinically relevant to measure outcomes after 9 months, because it takes at least 6 months for the toenail to regrow completely.

Comment: RCTs involving terbinafine frequently measured levels of liver enzymes and found that increases were asymptomatic, and reversed once the drug was stopped. Adverse events unique to terbinafine include sensory loss such as taste, smell, or hearing disturbance (see option on oral griseofulvin, p 12 and option on oral itraconazole, p 3).

High-risk populations:
Several prospective cohort studies have considered the safety of terbinafine to treat fungal nail infections in high-risk populations. One review paper reported the results of three studies involving people with diabetes mellitus, two studies in people with HIV infection, and two studies involving organ transplant recipients. [21] The review found that no significant adverse effects were reported in the diabetes studies. No drug interactions were reported in people receiving terbinafine, and glucose levels were unchanged during the treatment period (207 people receiving 250 mg/day of terbinafine for 12 weeks). The review found that the HIV studies reported no serious adverse effects (10 people receiving terbinafine 250 mg/day for 12 weeks, 21 people receiving terbinafine 250 mg/day for 16 weeks). It found that blood ciclosporin levels significantly decreased in organ transplant patients taking terbinafine, but this did not cause significant clinical change in the people or lead to organ rejection. Renal function remained normal (11 people receiving terbinafine 250 mg/day for 12 weeks, 4 receiving 250 mg/day terbinafine for 4–24 weeks). One open-label prospective study examined the safety of terbinafine use in people aged >60 years with onychomycosis of the feet confirmed by positive mycological culture. [22] It found that a total of 18 adverse events occurred, all considered mild to moderate in severity and transient in nature. No participants withdrew from the study because of adverse events (30 people receiving 250 mg/day for 12 weeks). The study also considered the 16 people taking drugs metabolised by the cytochrome P-450 isoenzyme 2D6, because of specific in vitro data suggesting a potential interaction between terbinafine and drugs metabolised by this isoenzyme. No drug interactions between these cases and terbinafine were observed.

See comment on oral griseofulvin, p 12 .

OPTION FLUCONAZOLE (ORAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- Oral fluconazole seems to modestly improve cure rates.

Benefits and harms

Oral fluconazole versus placebo:
We found one systematic review (search date 2000, 2 RCTs). [16]

Cure rates

Compared with placebo Oral fluconazole may be more effective at curing fungal toenail infection after 16 to 52 weeks' treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[16] Systematic review	331 people with fungal toenail infection Data from 1 RCT	**Cure rates , 16 weeks** 31% with oral fluconazole 150 mg weekly 7% with placebo Absolute numbers not reported	ARI 24% 95% CI 12% to 35%	○○○	oral fluconazole
[16] Systematic review	331 people with fungal toenail infection Data from 1 RCT	**Cure rates , 26 weeks** 48% with oral fluconazole 150 mg weekly 7% with placebo Absolute numbers not reported	ARI 40% 95% CI 28% to 52%	○○○	oral fluconazole
[16] Systematic review	331 people with fungal toenail infection Data from 1 RCT	**Cure rates , 39 weeks** 53% with oral fluconazole 150 mg weekly 7% with placebo Absolute numbers not reported	ARI 46% 95% CI 34% to 58%	○○○	oral fluconazole
[16] Systematic review	361 people with fungal toenail infection Data from 1 RCT	**Cure rates** 43% with oral fluconazole 150 mg weekly 13% with placebo Absolute numbers not reported	ARI 30% 95% CI 17% to 42%	○○○	oral fluconazole
[16] Systematic review	361 people with fungal toenail infection Data from 1 RCT	**Cure rates** 47% with oral fluconazole 300 mg weekly 13% with placebo Absolute numbers not reported	ARI 35% 95% CI 22% to 47%	○○○	oral fluconazole
[16] Systematic review	361 people with fungal toenail infection Data from 1 RCT	**Cure rates** 51% with oral fluconazole 450 mg weekly 13% with placebo Absolute numbers not reported	ARI 38% 95% CI 25% to 50%	○○○	oral fluconazole

Patient satisfaction

No data from the following reference on this outcome. [16]

Adverse effects

No data from the following reference on this outcome. [16]

Oral fluconazole versus oral griseofulvin:

We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral fluconazole versus oral itraconazole:

We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral fluconazole versus oral terbinafine:

We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral fluconazole versus oral ketoconazole:

We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral fluconazole versus topical treatments:

We found no systematic review or RCTs. We found one longitudinal study comparing oral antifungals versus topical treatments (see comment on oral griseofulvin, p 12).

Further information on studies

Comment: See comment on oral griseofulvin, p 12 .

OPTION GRISEOFULVIN (ORAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- Alternative oral antifungal treatments such as griseofulvin may increase cure rates of fungal toenail infection, but the evidence is insufficient to allow us to say for certain.

Benefits and harms

Oral griseofulvin versus placebo:

We found one systematic review (search date 2000), which found no RCTs. [16]

Oral griseofulvin versus oral itraconazole:

We found one systematic review (search date 2000, 3 RCTs). [16]

Cure rates

Oral griseofulvin compared with oral itraconazole Oral griseofulvin and oral itraconazole may be equally effective at curing fungal toenail infection after 24 to 72 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[16] Systematic review	19 people with fungal toenail infection Data from 1 RCT	**Cure rates , 24 weeks** 0% with griseofulvin 500 mg daily 0% with itraconazole 100 mg daily Absolute numbers not reported	ARR 0% 95% CI –17% to +18%	⟷	Not significant
[16] Systematic review	61 people with fungal toenail infection Data from 1 RCT	**Cure rates , 40 weeks** 30% with 24 to 36 weeks of griseofulvin 500 mg daily 37% with 24 to 36 weeks of itraconazole 100 mg daily Absolute numbers not reported	ARR +5% 95% CI –18% to +28%	⟷	Not significant
[16] Systematic review **3-armed trial**	108 people with fungal toenail infection Data from 1 RCT The remaining arm evaluated 72 weeks of griseofulvin 990 mg daily	**Cure rates , 77 weeks** 6% with 72 weeks of griseofulvin 660 mg daily 8% with 72 weeks of itraconazole 100 mg daily Absolute numbers not reported	ARR +2% 95% CI –8% to +10%	⟷	Not significant
[16] Systematic review **3-armed trial**	108 people with fungal toenail infection Data from 1 RCT The remaining arm evaluated 72 weeks of griseofulvin 660 mg daily	**Cure rates , 77 weeks** 6% with 72 weeks of griseofulvin 990 mg daily 8% with 72 weeks of itraconazole 100 mg daily Absolute numbers not reported	ARR +2% 95% CI –8% to +10%	⟷	Not significant

Patient satisfaction

No data from the following reference on this outcome. [16]

Adverse effects

No data from the following reference on this outcome. [16]

Oral griseofulvin versus oral terbinafine:

We found one systematic review (search date 2000, 3 RCTs). [16]

Cure rates

Oral griseofulvin compared with oral terbinafine Oral griseofulvin for 24 to 52 weeks may be less effective than oral terbinafine at curing fungal toenail infection (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[16] Systematic review	120 people with fungal toenail infection Data from 1 RCT	**Cure rates , 52 weeks** 63% with oral griseofulvin 1000 mg daily 75% with oral terbinafine 250 mg daily Absolute numbers not reported	ARR 12% 95% CI 4% to 28%	○○○	oral terbinafine
[16] Systematic review	171 people with fungal toenail infection Data from 1 RCT	**Cure rates , 72 weeks** 47% with 24 weeks of oral griseofulvin 1000 mg daily 62% with 24 weeks of oral terbinafine 250 mg daily Absolute numbers not reported	ARR 15% 95% CI 0% to 30%	○○○	oral terbinafine
[16] Systematic review	84 people with fungal toenail infection Data from 1 RCT	**Cure rates , 52 weeks** 46% with 52 weeks of oral griseofulvin 500 mg daily 84% with 16 weeks of oral terbinafine 250 mg daily Absolute numbers not reported	ARR 37% 95% CI 17% to 55%	○○○	oral terbinafine

Patient satisfaction

No data from the following reference on this outcome. [16]

Adverse effects

No data from the following reference on this outcome. [16]

Oral griseofulvin versus oral ketoconazole:

We found one systematic review (search date 2000, 3 RCTs). [16]

Cure rates

Oral griseofulvin compared with oral ketoconazole Oral griseofulvin and oral ketoconazole may be equally effective at curing fungal toenail infection after 24 to 49 weeks' treatment (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[16] Systematic review	16 people with fungal toenail infection Data from 1 RCT	**Cure rates , 49 weeks** 0% with oral griseofulvin 11% with oral ketoconazole Absolute numbers not reported	ARI +11% 95% CI –25% to +43%	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[16] Systematic review	26 people with fungal toenail infection Data from 1 RCT	**Cure rates , 24 weeks** 42% with oral griseofulvin 1000 mg daily 36% with oral ketoconazole 200 mg daily Absolute numbers not reported	ARR –6% 95% CI –38% to +27%	⟷	Not significant

Patient satisfaction

No data from the following reference on this outcome. [16]

Adverse effects

No data from the following reference on this outcome. [16]

Oral griseofulvin versus oral fluconazole:
We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral griseofulvin versus topical treatments:
We found no systematic review or RCTs. We found one longitudinal study comparing oral antifungals versus topical treatments (see comment). [23]

Further information on studies

Comment: The review [16] included 32 RCTs, 22 of which were funded by the pharmaceutical industry. All 22 of these RCTs produced data that supported the sponsor's product. The reviewers highlighted the possibility that the conclusions of the review were compromised by a publication bias. The review found that the definitions of clinical cure in the included RCTs were so diverse and inconsistent that it was not possible to make meaningful comparisons between clinical cure rates reported in the RCTs.

The review did not describe adverse effects of different oral antifungals separately. [16] A total of 31 of the 32 included RCTs examining oral antifungals reported on adverse events. The most common adverse effects were gastrointestinal complaints (such as diarrhoea), rash, and respiratory complaints. It was rare for people to withdraw from an RCT because of adverse effects, although treatment was sometimes interrupted. The review found no significant difference in the frequency of adverse events between oral antifungals and placebo (reported as not significant; numbers not reported).

Oral antifungals versus topical treatment:
We found one longitudinal study of 150 people with onychomycosis treated with mechanical (nail debridement), topical (clotrimazole, Fungi-Nail), and oral (terbinafine, itraconazole, fluconazole)

treatments. [23] People who had taken oral antifungal drugs reported significantly fewer onychomycosis-related problems (including embarrassment, self-consciousness, and being perceived as unclean by others) 9 months after treatment, compared with those receiving non-oral treatments. Satisfaction was significantly greater among people who had received oral drugs than non-oral treatment.

OPTION KETOCONAZOLE (ORAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- Alternative oral antifungal treatments such as ketoconazole may increase cure rates in people with fungal toenail infections, but the evidence is insufficient to allow us to say for certain.

Benefits and harms

Oral ketoconazole versus placebo:

We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral ketoconazole versus oral griseofulvin:

See option on oral griseofulvin, p 12 .

Oral ketoconazole versus oral itraconazole:

We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral ketoconazole versus oral terbinafine:

We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral ketoconazole versus oral fluconazole:

We found one systematic review (search date 2000), which identified no RCTs. [16]

Oral ketoconazole versus topical treatments:

We found no systematic review or RCTs. We found one longitudinal study comparing oral antifungals versus topical treatments (see comment on oral griseofulvin, p 12).

Further information on studies

Comment:

Hepatotoxicity:

We found one clinical case review of 3600 people by a pharmaceutical company in 1983. [24] The pharmaceutical company identified 77 cases of symptomatic hepatotoxicity during ketoconazole treatment; men and women were equally affected, but only the woman described below died. The review included one case report of fatal hepatitis in a previously healthy 67-year-old woman who received ketoconazole 200 mg daily for 2 months. We found a further case report of fatal hepatocyte necrosis in a 38-year-old woman receiving ketoconazole 200 mg daily for 103 days. [25] After stopping treatment, she developed signs and symptoms of liver failure and died.

See comment on oral griseofulvin, p 12 .

QUESTION What are the effects of topical treatments for fungal toenail infections?

OPTION CICLOPIROX (TOPICAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- Topical ciclopirox seems to modestly improve symptoms of fungal toenail infection compared with placebo.

Benefits and harms

Topical ciclopirox versus placebo:

We found one systematic review (search date 2005) [26] and one subsequent RCT. [27]

Cure rates

Compared with placebo Topical ciclopirox applied for 48 weeks is more effective at increasing cure rates (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
[26] Systematic review	468 people with fungal toenail infection 2 RCTs in this analysis	**Proportion of people who were not cured , 48 weeks** 22/229 (10%) with topical ciclopirox 71/239 (30%) with placebo For details of regimens, see further information on studies	RR 0.32 95% CI 0.20 to 0.52	●●○	topical ciclopirox
[27] RCT **3-armed trial**	467 people, 73% women, with fungal toenail infection The remaining arm assessed ciclopirox (hydrolacquer)	**Proportion of people cured , 48 weeks** 168/185 (91%) with ciclopirox (traditional lacquer) 64/95 (69%) with placebo 280 people in this analysis; single-blind study Cure defined as conversion to negative culture See further information on studies	P = 0.0001	○○○	ciclopirox (traditional lacquer)
[27] RCT **3-armed trial**	467 white people, 73% women, with fungal toenail infection The remaining arm assessed ciclopirox (traditional lacquer)	**Proportion of people cured , 48 weeks** 156/175 (89%) with ciclopirox (hydrolacquer) 64/95 (69%) with placebo 270 people in this analysis; single-blind study Cure defined as conversion to negative culture See further information on studies	P = 0.0001	○○○	ciclopirox (hydrolacquer)

Patient satisfaction

No data from the following reference on this outcome. [26] [27]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] RCT	Number of people included unclear In review [26]	**Adverse effects** 11% with topical ciclopirox 7% with placebo Absolute numbers not reported Adverse effects included tingling sensation, changes in nail shape or colour, and localised erythema	Significance not assessed		
[27] RCT **3-armed trial**	467 white people, 73% women, with fungal toenail infection	**Proportion of people with mild adverse effects , 48 weeks** 11% with ciclopirox (hydrolacquer) 25% with ciclopirox (traditional lacquer) 20% with placebo Absolute numbers not reported See further information on studies	Significance not assessed		

No data from the following reference on this outcome. [26]

Topical ciclopirox versus other topical antifungal treatments:

We found no RCTs comparing topical ciclopirox versus other topical antifungal treatments.

Topical ciclopirox versus oral treatments:

We found one RCT (see option on oral terbinafine, p 7). We also found one longitudinal study comparing topical treatments versus oral antifungals (see comment on oral griseofulvin, p 12).

Further information on studies

[26] In one RCT included in the review, people were advised to coat the entire toenail with lacquer, including the entire nail plate and 5 mm of surrounding skin. Participants were advised to wait at least 8 hours before washing the nails, and not to remove the coat from the previous day but to apply new coats over the old. Every 7 days, isopropyl alcohol swabs were used to remove the build-up of lacquer.

[27] The RCT primarily assessed the superiority to placebo and non-inferiority to traditional ciclopirox lacquer of ciclopirox hydrolacquer, an "innovative water-soluble biopolymer". The new ciclopirox hydrolacquer is described as being easier to use as it can be removed by daily rinsing with water rather than requiring isopropyl alcohol swabs at the end of each treatment week. In vitro studies suggested a greater affinity to keratin and nail permeation. The RCT used last observation carried forward (LOCF) analyses for people who completed at least 6 months of treatment.

Comment: The RCT comparing the new preparation of ciclopirox hydrolacquer [27] also considered complete cure (negative culture, negative microscopy, and 100% nail clearance) as an outcome. After 48 weeks' treatment there was no significant difference in complete cure between the new preparation

and the traditional lacquer (10/175 [6%] with hydrolacquer *v* 6/185 [3%] with traditional lacquer; P = 0.68). But the difference in complete cure was significant after a further 12-week review period (20/157 [13%] with hydrolacquer *v* 9/156 [6%] with traditional lacquer; P <0.05). This showed that, although a high proportion of people were achieving negative culture and microscopy with the new and traditional ciclopirox preparations (about 90%), a much smaller proportion (13%) had normal looking nails after 1 year of treatment.

OPTION MECHANICAL DEBRIDEMENT

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- We found no clinically important results from RCTs about the effects of mechanical debridement in fungal toenail infection.

Benefits and harms

Mechanical debridement:

We found no systematic review or RCTs. We found one longitudinal study comparing oral antifungals versus topical treatments (see comment on oral griseofulvin, p 12).

Further information on studies

Comment:

We found one open-label study (504 people aged >65 years) comparing terbinafine 250 mg daily for 12 weeks alone versus terbinafine 250 mg daily plus mechanical debridement. [29] The RCT reported that 75 (43%) people reported adverse effects. These included ingrowing toenails (5%), sinusitis (5%), nausea (4%), and headache (1%). The study did not describe in which treatment arm these adverse effects occurred, or give absolute numbers, and no significance assessments were performed. Overall, 4% of the study group withdrew from the trial due to adverse effects. In the terbinafine group, one person withdrew due to nausea/headaches. In the terbinafine-plus-debridement group, two people withdrew due to nausea/headache and flank pain. [29]

Mechanical (aggressive) debridement involved removal of the unattached distal portion of the nail plate and debridement of the infected nail plate using nail nippers or a nail drill or both. [29] This was performed at intervals from baseline up to 48 weeks. No avulsion under anaesthetic was involved. [29]

We found one open-label RCT (55 people, 289 toenails) comparing debridement alone versus debridement plus topical ciclopirox for a median of 10.5 months. [30] Treatment was randomised by participant, but analysed by number of toenails. The RCT found that cure rates, defined as negative culture, were 0/160 (0%) toenails with debridement alone compared with 99/129 (77%) toenails with debridement plus ciclopirox.

The RCT also considered the outcome of foot health measured on the 15-item Bristol Foot Score. A lower score reflects an improvement in perceived foot health. [30] A significant difference in the change in perceived foot health was shown with debridement combined with ciclopirox (55 people; –7.5 with debridement alone *v* –9 with debridement plus ciclopirox; P = 0.0002).

OPTION AMOROLFINE (TOPICAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- We found no clinically important results from RCTs about the effects of topical amorolfine in fungal toenail infection.

Benefits and harms

Topical amorolfine:

We found one systematic review (search date 2005), which identified no RCTs. [26] We found no subsequent RCTs comparing topical amorolfine versus placebo or other topical antifungal treatments.

Topical amorolfine plus oral terbinafine versus oral terbinafine:
See option on oral terbinafine versus topical treatments, p 7 .

Further information on studies

Comment: None.

OPTION BUTENAFINE (TOPICAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- We found no clinically important results from RCTs about the effects of topical butenafine in fungal toenail infection.

Benefits and harms

Topical butenafine:
We found one systematic review (search date 2005), which identified no RCTs. [26] We found no subsequent RCTs comparing topical butenafine versus placebo or other topical antifungal treatments.

Further information on studies

Comment: None.

OPTION FLUCONAZOLE (TOPICAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- We found no clinically important results from RCTs about the effects of topical fluconazole in fungal toenail infection.

Benefits and harms

Topical fluconazole:
We found one systematic review (search date 2005), which identified no RCTs. [26] We found no subsequent RCTs comparing topical fluconazole versus placebo or other topical antifungal treatments.

Further information on studies

Comment: None.

OPTION KETOCONAZOLE (TOPICAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- We found no clinically important results from RCTs about the effects of topical ketoconazole in fungal toenail infection.

Benefits and harms

Topical ketoconazole:

We found one systematic review (search date 2005), which identified no RCTs. [26] We found no subsequent RCTs comparing topical ketoconazole versus placebo or other topical antifungal treatments.

Further information on studies

Comment: None.

OPTION TERBINAFINE (TOPICAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- We found no clinically important results from RCTs about the effects of topical terbinafine in fungal toenail infection.

Benefits and harms

Topical terbinafine:

We found one systematic review (search date 2005), which identified no RCTs. [26] We found no subsequent RCTs comparing topical terbinafine versus placebo or other topical antifungal treatments.

Further information on studies

Comment: None.

OPTION TIOCONAZOLE (TOPICAL)

- For GRADE evaluation of interventions for Fungal toenail infections, see table, p 24 .
- We found no clinically important results from RCTs about the effects of topical tioconazole in fungal toenail infection.

Benefits and harms

Topical tioconazole:

We found one systematic review (search date 2005), which identified no RCTs. [26] We found no RCTs comparing topical tioconazole versus placebo or other topical antifungal treatments.

Further information on studies

Comment: None.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Ciclopirox (topical) New evidence added. [27] Categorisation unchanged (Likely to be beneficial).

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Competing interests: JF declares that she has no competing interests.

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GRADE **Evaluation of interventions for Fungal toenail infections.**

Important outcomes			Cure rates, Patient satisfaction						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of oral treatments for fungal toenail infections?									
3 (433) [16]	Cure rates	Oral itraconazole versus placebo	4	–3	0	0	0	Very low	Quality points deducted for short follow-up, possibility of publication bias, and inconsistent definitions of cure
5 (881) [16] [17]	Cure rates	Oral itraconazole versus oral terbinafine	4	–2	–1	0	0	Very low	Quality points deducted for possibility of publication bias and inconsistent definitions of cure. Consistency point deducted for conflicting results
3 (235) [16]	Cure rates	Pulsed versus continuous itraconazole	4	–2	0	0	0	Low	Quality points deducted for possibility of publication bias and inconsistent definitions of cure
799 (5) [16]	Cure rates	Oral terbinafine versus placebo	4	–3	0	0	0	Very low	Quality points deducted for possibility of publication bias, short follow-up, and inconsistent definitions of cure
1 (73) [19]	Cure rates	Oral terbinafine versus topical treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (692) [16]	Cure rates	Oral fluconazole versus placebo	4	–2	0	0	0	Low	Quality points deducted for possibility of publication bias and inconsistent definitions of cure
3 (188) [16]	Cure rates	Oral griseofulvin versus oral itraconazole	4	–3	0	0	0	Very low	Quality points deducted for sparse data, possibility of publication bias, and inconsistent definitions of cure
3 (375) [16]	Cure rates	Oral griseofulvin versus oral terbinafine	4	–2	0	0	0	Low	Quality points deducted for possibility of publication bias and inconsistent definitions of cure
2 (42) [16]	Cure rates	Oral griseofulvin versus oral ketoconazole	4	–3	0	0	0	Very low	Quality points deducted for sparse data, possibility of publication bias, and inconsistent definitions of cure
What are the effects of topical treatments for fungal toenail infections?									
3 (935) [26] [27]	Cure rates	Topical ciclopirox versus placebo	4	0	0	0	0	High	

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.